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Updated Review of Blood Culture Contamination

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INTRODUCTION

The blood culture represents a critical tool for the health care professional as a means of detecting the dangerous presence of living organisms in the bloodstream. A positive blood culture can suggest a definitive diagnosis, enable the targeting of therapy against the specific organism(s) in question, and provide prognostic value (22). Like any test, however, false-positive results can limit the utility of this important tool. In blood cultures, false positives arise due to contamination, which occurs when organisms that are not actually present in a blood sample are grown in culture. Contaminated cultures have been recognized as a troublesome issue for decades and continue to be a source of frustration for clinical and laboratory personnel alike. Faced with a positive blood culture result, clinicians must determine whether the organism represents a clinically significant infection associated with great risk of morbidity and mortality or a false-positive result of no clinical consequence. Further complicating the issue in recent years is the increasing use of central venous catheters (CVC) and other indwelling vascular access devices (5, 90). Interpretation of culture results for patients with these devices in place is particularly challenging because while these individuals are at increased risk for bacteremia, such results may also indicate culture contamination or colonization of the line. The clinical uncertainty associated with the interpretation of ambiguous culture results is costly, as has been demonstrated in a number of studies of both adult and pediatric patients (13, 115, 125, 138).

Prevalence and Significance

While target rates for contamination have been set at 2 to 3% (30, 131), actual rates seem to vary widely between institutions, from as little as 0.6% to over 6% (13, 64, 67, 82, 89, 112, 113, 125, 131, 150). The College of American Pathologists (CAP) Q-Probes quality improvement study involved the prospective examination of 497,134 blood culture specimens from 640 U.S. health care institutions (113). While the median adult inpatient contamination rate was 2.5%, some organizations had a rate of less than 1.0%, while for other organizations, more than 5.0% of their blood cultures were contaminated. More recently, the CAP Q-Tracks study found an overall median contamination rate of 2.92% for data collected from 356 institutions from 1999 to 2003. There is also some evidence to suggest that in recent decades, these rates have been on the increase (150), although the Q-Tracks study found no increase over the 4-year time frame for their data. The suggested reasons for this increase include technological advances that allow the detection of smaller quantities of living microorganisms in the blood, the increased use of indwelling catheters for the

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TABLE 1. Addressing the challenge of blood culture contamination

Approach	Rationale
Detecting contaminants	Given that contamination can likely never be eliminated, having reliable factors to help identify true positives vs false positives is critical for patient management and population-based surveillance
Prevention	Reducing contamination rates will improve the specificity of the blood culture and result in a higher PPV, resulting in a significantly more useful test
Supporting optimal use of blood cultures	Reducing the use of blood cultures in patients with a very low likelihood of bacteremia will result in a higher PPV and reduced costs associated with contamination; pretest probability of bacteremia can be estimated using population-based studies of disease prevalence or clinical prediction rules

provision of therapy, and changes in phlebotomy practices to minimize the risk of needlestick injuries (151).

The financial impact of blood culture contamination has been described in a number of studies (13, 35, 125, 145). Bates et al. found that contaminant results, compared with true-negative results, were independently associated with increased subsequent laboratory charges (20% increase) and intravenous antibiotic charges (39% increase) (13). In a subsequent prospective study focused on blood culture contamination caused by coagulase-negative staphylococci, Souvenir et al. reported that almost half of the patients with a false-positive result were treated with antibiotics, often with vancomycin (125). According to their estimates, the additional costs associated with this unnecessary treatment were approximately $1,000 per patient. Other investigators focused on the consequences of contaminated cultures in pediatric populations (115, 138). Segal and Chamberlain estimated that the additional charges associated with contaminated cultures in 85 children aged 3 to 36 months who were evaluated in an emergency department and believed to be at risk for occult bacteremia totaled $78,904, the majority of which was due to subsequent hospital admission (115). In a retrospective study of 9,959 blood cultures performed in children aged 1 month to 18 years, Thuler et al. found that 26% of children with false-positive cultures who were initially evaluated as outpatients were subsequently admitted to the hospital on the basis of initial culture results (138). Measured in costs or charges, there is compelling evidence that the financial impact of blood culture contamination is significant.

Given these excessive costs, how can we address the problem of contaminated blood cultures? There has been significant effort in recent years to attempt to identify ways of preventing contamination in the first place. In addition, investigators have studied factors that help distinguish true positives from false positives. Since a major consequence of contaminated cultures is a lower positive predictive value (PPV) for the blood culture test, and the pretest probability of bacteremia is a key determinant of PPV (6), there have been increasing endeavors to discourage the utilization of blood cultures in patients at very low risk for this disease. For example, clinical bacteremia prediction rules have been developed and studied to help guide clinical decision-making in the use and interpretation of blood cultures and the initiation of empirical antibiotic therapy. In addition, population-based studies of bacteremia prevalence for specific patient groups have been performed in the past decade. Such information, while not completely individualized to a given patient, provides a rough estimate of pretest probability for bacteremia. In summary, the challenge of blood culture contamination can be addressed by at least three different avenues of approach, as summarized in Table 1.

In the last decade, significant progress has been made in each of these three broad areas. New evidence for measures to reduce contamination rates is emerging, and we are becoming better able to ascertain bacteremia risk at both the individual and patient population levels. In addition, much has been learned about how to accurately distinguish between true bacteremia and contamination. In this review, we provide an updated analysis of this important, complex topic with special attention paid to each of these areas. We also highlight specific challenges associated with blood culture contamination in the pediatric population, although an in-depth analysis is beyond the scope of our review.

DETECTION OF CONTAMINATED BLOOD CULTURES

Despite its limitations, the blood culture remains the "gold standard" for the detection of bacteremia. An accurate interpretation of culture results is critical not only from the perspective of individual patient care but also from the standpoint of hospital epidemiology and public health. The tracking and reporting of nosocomial infections and monitoring of bloodstream infection rates are both essential infection control activities that depend heavily on the accurate differentiation of contamination from true bacteremia. Reliably making this determination continues to be very challenging for clinicians, epidemiologists, and microbiologists. In recent decades, multiple approaches have been studied, advocated, and utilized for this purpose. Clues that may help to differentiate contamination from bacteremia include identity of the organism, number of positive culture sets, number of positive bottles within a set, time to growth, quantity of growth, clinical and laboratory data, source of culture, and automated classification using information technology.

Identity of Organism

Often, the identity of the microbe that grows from a blood culture is a very helpful clue that the results may or may not represent contamination. The CAP Q-Probes study described above found that the most important indicator when interpreting blood culture results was the identity of the organism, which was cited as very important to 79% of laboratories (113). Bates et al. found that the identity of the organism was the most important predictor in a predictive model for differenti-

TABLE 2. False-positive rates for organisms that frequently represent contamination

Organism(s)	Source			
	1,585 blood culture-positive episodes from 3 U.S. hospitals[a]		497,134 blood cultures from 640 U.S. institutions[b]	
	% of all positive cultures (n = 1,585)	Contamination rate (%)	% of all positive cultures	Contamination rate (%)
Coagulase-negative staphylococci	44.3	82	Not reported	62–63
Corynebacterium spp. (other than *C. jeikieum*)	33.4	96	Not reported	68–78
Bacillus spp.	0.8	91.7	Not reported	68–70 (other than *B. anthracis*)
Propionibacterium acnes	3.0	100	Not reported	84–85
Viridans group streptococci	4.5	49.3	Not reported	32–33
Clostridiium perfringens	0.8	76.9	Not reported	Not reported

[a] Data are from reference 155.
[b] Data are from reference 113.

ating contaminated blood culture results from results indicating bacteremia (14).

Weinstein et al.'s study of 843 episodes of positive blood cultures in adult inpatients from three hospitals around the country suggested that certain organisms should almost always be thought to represent true bacteremia or fungemia when isolated from a blood culture (155). These organisms included *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and other *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Candida albicans*. Furthermore, Weinstein's personal observation is that the following organisms almost always represent a true infection when isolated from a blood culture: *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, members of the *Bacteroides fragilis* group, all *Candida* species, and *Cryptococcus neoformans* (151).

Along the same vein, certain organisms have been found to represent contamination in a significant proportion of cases. These organisms include coagulase-negative staphylococci, *Corynebacterium* species, *Bacillus* species other than *Bacillus anthracis*, *Propionibacterium acnes*, *Micrococcus* species, viridans group streptococci, enterococci, and *Clostridium perfringens* (151, 155). However, it is crucial to recognize that each of these organisms can also represent true bacteremias with devastating consequences, particularly if untreated due to misinterpretation as contaminants. Of these organisms, the ones that are thought to represent true bacteremia only rarely are *Corynebacterium* species, *Bacillus* species other than *B. anthracis*, and *Propionibacterium acnes* (151, 155). In addition to the work of Weinstein et al., the CAP Q-Probes study provided valuable information on contamination rates for organisms that frequently represent contamination (Table 2).

Despite the high likelihood that certain organisms usually represent contaminants when isolated from blood cultures, determining the likelihood of true bacteremia can be challenging for clinicians. Coagulase-negative staphylococci represent an important, all-too-frequent case in point. In the past, coagulase-negative staphylococci were usually believed to represent contamination when isolated from blood cultures. In fact, coagulase-negative staphylococci are the most common blood culture contaminants, typically representing 70% to 80% of all contaminated blood cultures (25, 92, 105, 113, 125).

Recently, however, studies have shown that these organisms are an increasing source of true bacteremia in patients with prosthetic devices and central venous catheters (30, 53, 105, 139, 155), although the majority of isolates of coagulase-negative staphylococci from blood cultures continue to be contaminants. Weinstein et al. found that even though only 12.4% of coagulase-negative staphylococcal isolates were clinically significant, they ranked as the third most common cause of bacteremia because of their high prevalence (155). In another study, among 81 episodes of coagulase-negative staphylococcal blood culture results, the incidence of clinically significant bacteremia was 20 (24.7%) episodes, that of indeterminate bacteremia was 10 (12.3%) episodes, and that of contamination was 59 (72.8%) episodes (125). Other studies found rates of true bacteremias ranging from 10% to 26.4% when coagulase-negative staphylococci are isolated from blood cultures (51, 125).

Similarly, other organisms can be difficult to interpret when isolated from blood cultures. One study found that enterococci were pathogens 70% of the time, whereas viridans group streptococci were pathogens 38% of the time (155). Furthermore, that same study found that *Clostridium perfringens* was a contaminant 77% of the time, whereas other *Clostridium* species were true pathogens 80% of the time. Given these data, clinicians attempting to differentiate true infections from simply contaminated blood cultures cannot rely solely on the identity of the organism.

Often, bloodstream infections involve only a single organism, prompting clinicians to sometimes conclude that a blood culture bottle that grows multiple organisms is contaminated. However, studies have found that 6% to 21% of all true bacteremias are polymicrobial, usually in patients in high-risk groups (121). Furthermore, multiple coagulase-negative species have been found to cause polyclonal coagulase-negative staphylococcal infections (42, 142, 143). Therefore, one cannot conclude that the mere presence of multiple organisms in a blood culture bottle always indicates contamination.

Number of Positive Blood Culture Sets

One proven methodology that can help differentiate blood culture contamination from true infection is the number of blood culture sets that grow organisms. The proportion of positive sets as a function of the total number of sets obtained can be a particularly useful tool (16, 69, 154, 155). If only one

set of at least two sets grows an organism known to often cause contamination, this often represents a contaminant. For true bacteremias, multiple blood culture sets will usually grow the same organism (53, 139, 155). In fact, this indicator is one of the most frequently used tools to help differentiate contamination from bacteremia as indicated in the CAP Q-Probes study, which revealed that 77% of laboratories cited the proportion of positive blood cultures in a series of cultures as very important for interpreting blood culture results (113). In their examination of 11,167 episodes in which coagulase-negative staphylococci were isolated from blood cultures, 27.8% were interpreted as contaminants if at least two sets were positive compared to 75.2% if only one of at least two sets were positive. In 2,440 cases, only a single blood culture was available; in these cases, 66.9% of the isolates were determined to be contaminants.

When multiple cultures are obtained and return positive, the positive predictive value for true bacteremia has been shown to improve (51). In one modeling study of patients with a central vascular line and a positive culture for coagulase-negative staphylococci, the positive predictive value was 55% when one of one culture was positive, 20% when one of two cultures was positive, and only 5% when one of three cultures was positive (139). In the face of such data, it has become increasingly clear that maximizing the diagnostic utility of blood cultures requires at least two sets be performed.

Because coagulase-negative staphylococci represent contaminants more often than true infections when isolated from blood culture bottles, even when two sets are positive for this organism, it can be difficult to determine whether both sets are contaminated as opposed to representing a true infection. Souvenir et al. found that only a single set of blood cultures was positive for 35% of samples from patients with coagulase-negative staphylococcal bacteremia, whereas two or more sets were positive for 12% of the patients in the contamination category (125).

Evidence based on molecular studies also highlights the fact that multiple positive culture results may be helpful but imperfect in discerning contamination. An approach using pulsed-field gel electrophoresis (PFGE) was explored in 14 febrile neutropenic patients who had matched peripheral and catheter-drawn cultures that both grew *Staphylococcus epidermidis* (86). Of these 14 patients, 10 had identical or closely related strains, and the remaining 4 were thought to represent either mixed infection or contamination. Another study of 42 patients with at least two positive cultures for coagulase-negative staphylococci drawn within a 14-day interval found that PFGE plus arbitrary primed PCR detected the same strain in 19 (45%) cultures, suggesting that the 23 (55%) cultures that grew different strains were either contamination events or infections involving multiple strains of coagulase-negative staphylococci (117). In that study, patients with three or more positive blood cultures were significantly more likely to have same-strain bacteremia than those with only two positive cultures (11 [73%] of 15 versus 8 [30%] of 27; $P = 0.006$). A similar study that used clinical criteria to differentiate true bacteremia from contamination in 22 patients who had at least two positive cultures for coagulase-negative staphylococci found that only 1 of 41 blood cultures in bacteremic patients had an unrelated strain by PFGE, compared to 6 of 16 in contaminated samples (121). Their statistically significant findings provide further evidence that genotypic variation is more common in contaminated samples, and recurring identical strains of coagulase-negative staphylococcal are more likely to represent bacteremia.

Because molecular testing of culture isolates is not realistic in clinical practice, many clinicians use the antimicrobial susceptibility patterns to indicate whether the isolates represent identical strains (51, 58). In the aforementioned study, of the 14 patients who grew *S. epidermidis* from matching sets, 13 had identical susceptibility patterns, whereas 10 had identical or closely related PFGE patterns (as defined by $\leq$3 band differences), thereby indicating that three of the four patients who did not match on the basis of PFGE would have been misclassified as identical isolates if only antimicrobial susceptibility patterns had been used (86). Another study of paired blood culture isolates of identical species with identical MICs found that 9 to 18% of the isolates were actually distinctly different strains (121). Khatib et al. found that the antibiograms of all 21 episodes of true bacteremia (as indicated by molecularly identical coagulase-negative staphylococcal strains in multiple sets) were identical and that 7 (15.9%) of 44 unrelated pairs of coagulase-negative staphylococci had identical antibiograms (57). In that study, identical antibiograms, determined by using the individual MICs of 10 antibiotics, were highly predictive of strain relatedness, with a sensitivity of 100% and a specificity of 83.7%, and a fourfold difference in a single MIC was always predictive of strain variation even if the difference did not change the susceptibility category for the strain. Moreover, the specificity of the antibiogram was lower when nonquantitative methods were used, and the level of specificity correlated with the number of antibiotics compared.

Clearly, speciating any coagulase-negative staphylococci that grow from multiple blood cultures can help determine the likelihood of contamination, because if the species from one set differs from the species from the other set, the culture results indicate either mixed infection or contamination (153). However, speciation of coagulase-negative staphylococci is not always automatically performed by clinical microbiology laboratories. Indeed, one study found that only 20 (59%) of 34 hospitals surveyed routinely identified coagulase-negative staphylococci to the species level (105).

For these reasons, it has been recommended that multiple sets of blood cultures be obtained to work up potential bloodstream infections. The presence of only one positive set among at least two sets drawn at the same time may be indicative of culture contamination. Additionally, the presence of one positive set over several cultures drawn over a period of time may also indicate contamination, although it may conversely indicate transient bacteremia. In order to differentiate transient bacteremia from contamination, it has been recommended that at least two sets of cultures be obtained at the same time (6, 30, 53, 71, 102, 107, 118, 152).

However, obtaining at least two sets is not always done (93, 105, 111). In a study of 333 small public and private hospitals (median occupancy of 57), the median rate of obtaining only a solitary blood culture was 12.7%, and the rates for the 10th and 90th percentiles were 42.5% and 3.4%, respectively (93). The same study found that solitary blood culture rates were lower for institutions with phlebotomists, with institutional policies

that required at least two sets, with notification of ordering clinicians when only one set was ordered, and with quality control programs aimed at monitoring solitary blood cultures. In two broader Q-Probes studies described by Schifman et al., significant variation in the utilization of solitary blood cultures was also found. In 289,572 blood culture sets from 909 hospitals, those authors found median proportions of solitary blood cultures of 10.1% and 12.1% among adult inpatients, 25.4% and 33.3% among adult outpatients, and 89.0% and 100% among pediatric/infant patients in the two studies, respectively (111).

Number of Positive Blood Culture Bottles within a Blood Culture Set

Another method that has been used by health care workers to differentiate contaminated blood cultures from cultures that represent bacteremia is the number of blood culture bottles that exhibit growth within a given blood culture set. Theoretically, if only one bottle exhibits growth within a given set, the likelihood of contamination is greater. However, there is at least one study that suggested that these criteria should not be used for this purpose (84). In their study, Mirrett et al. found that the number of bottles positive for coagulase-negative staphylococci within blood culture sets comprising two, three, or four bottles was not correlated with the likelihood of infection using clinical parameters (84). Among 486 sets that were comprised of two bottles, the positive predictive value for sepsis was 18% when one bottle was positive versus 37% when both bottles were positive. Among 235 sets comprised of three bottles, the positive predictive value for sepsis was 28, 52, and 30% when one, two, and three bottles, respectively, were positive. For 303 sets comprised of four bottles, the positive predictive value was 27, 28, 19, and 27% when one, two, three, and four bottles, respectively, were positive. Those authors concluded that the number of positive bottles in a given set did not reliably predict clinically significant infection. Another study found that increasing numbers of positive bottles did predict the likelihood of true bacteremia as defined by clinical parameters: of 129 patients with coagulase-negative staphylococci isolated from a single venipuncture using sets comprised of four bottles, the positive predictive value for true infection was 2% when one bottle was positive, 9% when two bottles were positive, 13% when three bottles were positive, and 27% when all four bottles were positive (94).

Usually, a set of blood cultures involves one aerobic bottle and one anaerobic bottle in an attempt to optimize the isolation of both aerobic and anaerobic organisms. It makes sense intuitively that if growth of a given organism is more likely in aerobic conditions than anaerobic conditions, the number of positive culture bottles within a set that consists of one aerobic and one anaerobic bottle should not be used to differentiate contaminated from clinically significant cultures. Not surprisingly, recent studies have found that the presence of growth for a given organism varies between the aerobic and anaerobic bottles. One study of 644 positive blood culture sets found that 413 (59.8%) were recovered from both bottles, 206 (29.8%) were recovered only from the aerobic bottle, and 72 (10.4%) were recovered only from the anaerobic bottle (108). In that study, the aerobic bottle was significantly superior to the anaerobic bottle for both recovery and detection time for overall organisms, and there was no significant difference in detection time for facultative anaerobic bacteria between the two bottles. Another study of coagulase-negative staphylococcal isolates found that the majority (59.7%) of isolates grew in the aerobic bottle only, whereas 27.7% grew in both bottles and 12.6% grew only in the anaerobic bottle (57). Other studies have shown the same lower yields for anaerobic blood cultures (87).

Time to Growth (Time to Positivity)

Another factor in determining contamination that has been explored by several investigators is the amount of time required for the organism to grow in the culture medium. Conceptually, it is thought that perhaps the blood from a bacteremic patient will have a much higher inoculum of bacteria than a contaminated culture. Theoretically, it follows that a larger inoculum will grow faster than a smaller inoculum, a theory that seems to have been verified in prior studies of catheter-related bloodstream infections (28, 41, 48, 53, 104). In support of this theory, several studies have shown that cultures that become positive more than 3 to 5 days after incubation have been more likely to represent contaminants (37, 49, 50, 53, 62, 75, 103, 108). Because it can be difficult to obtain more than one set of cultures in the pediatric population, Haimi-Cohen et al. used clinical parameters to differentiate true coagulase-negative infections from contaminants and found that a time to positivity of $\leq$15 h had a positive predictive value of 84% for true infection in children (48).

Bates et al. found that the time to growth was a useful variable in a multivariate algorithm for predicting true bacteremia from a positive culture result, although it did not perform as well as either the identification of the organism or the presence of multiple positive cultures (14). Other studies have not found time to growth to be a useful parameter. Souvenir et al.'s study, which differentiated coagulase-negative staphylococcus-contaminated cultures from bacteremias using clinical parameters, found no significant difference between the contaminant group and the true bacteremia in the time to detection of a positive culture (125). Khatib et al.'s molecular study of 47 episodes of multiple positive cultures for coagulase-negative staphylococci found that time to growth did not help differentiate cultures that grew identical strains (2.1 ± 1.4 days) from culture sets that differed by strain (1.9 ± 0.9 days) (57).

In the CAP Q-Probes study, the difference in time to detection for contaminant versus true-positive coagulase-negative staphylococci was statistically significant but, as those authors pointed out, probably not clinically significant due in part to a substantial overlap in growth time (113). Furthermore, as the technology of continuous monitoring of blood cultures to detect growth advances, the time to growth and sensitivity for detecting growth can be expected to change, making the use of this technology in this regard questionable (77, 83). Thus far, some experts recommend that this technological variable should not be relied upon to distinguish contaminants from pathogens in blood cultures (151).

Quantity of Growth per Culture Bottle

Another method that has been used to determine the clinical significance of culture results is the quantity of growth in a given culture sample. This method has been used to differentiate sputum colonization from pneumonia, urine colonization from urinary tract infection, and catheter-related bloodstream infection from non-catheter-related bloodstream infection (2, 53, 106, 127, 128). However, limited data exist to support use of this methodology for differentiating contaminated blood cultures from truly positive blood cultures in adults. St. Geme III et al. found that quantitative cultures in conjunction with specific clinical information may distinguish sepsis from contamination with coagulase-negative staphylococci in young infants but cautioned that low colony counts should not be dismissed as contamination in this high-risk population (129).

Clinical and Laboratory Clues

Others have recommended that the addition of clinical information is essential to appropriately classify positive blood culture results (14, 43, 48, 51, 69). Studies have found that clinicians often diagnose infection when rigid laboratory-based algorithms for differentiating contamination from bacteremia would not have diagnosed infection. The CAP Q-Probes study noted that the median contamination rate differed depending upon whether a clinical assessment was used to make the determination (2.1%) versus laboratory assessment (2.5%) (113). In that study, when coagulase-negative staphylococci were isolated from only one of at least two sets, 84.3% of the cases were interpreted as contaminants by using laboratory methods compared to 73.9% by using laboratory and clinical evaluation.

Many clinicians use fever and other signs of sepsis syndrome to help with the interpretation of positive blood cultures. Weinstein et al. found that hypothermia (temperature of <36°C) or marked fever (temperature of >40°C), leukocyte counts of <4,000 leukocytes/μl or >20,000 leukocytes/μl, and hypotension predicted true infection as opposed to contamination (155). However, another study found that fever at the onset of a blood culture positive for *Staphylococcus epidermidis* did not help differentiate true bacteremia from contamination in leukemic patients (68). Other studies have found similar results in which sepsis-like syndromes, including fever, did not help differentiate episodes thought to be contaminants from true bacteremias (118).

Clinical criteria combined with laboratory data have been used in several studies to differentiate contaminated cultures from clinically significant cultures (14, 30, 43, 51, 59, 125, 129, 155). Bates et al. developed a multivariate algorithm utilizing many predictors, one of which was a "clinical risk score," which consisted of fever, rigors, outcome, intravenous drug abuse, acute abdomen, and comorbidities as variables (14). This clinical risk score was found to be predictive of contamination, as was the organism type, days to culture positivity, and the presence of multiple positive cultures. Khatib et al.'s molecular analysis of 47 episodes of coagulase-negative staphylococcus-positive cultures found that strain relatedness was more frequent in patients who had a fever (15 [71.4%] of 21), an identifiable source (7 [77.8%] of 9), or a bacteremia that met the definition of nosocomial acquisition (18 [50%] of 36) (57). The presence of an identifiable source, specifically, a central venous catheter, was found to be predictive of true bacteremia in another study as well (68).

National Nosocomial Infection Surveillance (NNIS) parameters and surveillance criteria often utilize the treating clinician's diagnosis of bloodstream infection to differentiate true bacteremia from contamination for common contaminants (43). However, one study that correlated cultures that grew the same strain of coagulase-negative staphylococci with the clinician's suspicion/treatment found that the classification of coagulase-negative staphylococcal bacteremias as the same strain correlated poorly with the clinical assessment utilizing the clinician's diagnosis (117). Furthermore, in another study, even though treating clinicians and reviewers who performed retrospective analyses agreed on 100% of coagulase-negative staphylococcal bacteremias and 95% of contaminations, one-half of patients with contaminated blood cultures were still treated with antibiotics, leading to vancomycin misuse in 34% of patients (125). Of course, this may be related to a lower threshold for interpreting an uncertain result as an infection until proven otherwise in the presence of a gravely ill patient rather than true disagreements about what represents contamination.

Other surrogate markers for infection have been studied as well, including the use of C-reactive protein measurements. In neonates, a single C-reactive protein obtained at least 12 h after the onset of symptoms has been found to be helpful to diagnose clinical sepsis (18, 98, 110). In another study of leukemic patients, the level of a single C-reactive protein did not help differentiate between contamination and bacteremia, but the median increase in C-reactive protein over 24 h from the first positive blood culture did help (68). Given these data, some neonatal intensive care unit (NICU) clinicians are beginning to utilize C-reactive protein for this purpose: a survey of 35 NICUs found that C-reactive proteins were routinely obtained at 23% of NICUs and by 30% of NICU clinicians (105).

Source of Cultures (Catheter Drawn versus Percutaneous)

When blood cultures drawn from a vascular catheter are positive, the results could indicate one of three possibilities: true bacteremia, catheter colonization, or culture contamination. Catheter colonization is not contamination, nor is it infection—it occurs when microorganisms grow on the surface of a catheter such that the colonizing organisms would be expected to grow in blood samples obtained from the catheter (in contrast to culture contamination). Catheter colonization may or may not progress to cause symptoms of infection or true bacteremia. Studies have shown that 15 to 25% of short-term central venous catheters are colonized, usually by coagulase-negative staphylococci, and most patients have no evidence of infection (46, 133). Therefore, cultures drawn from central lines could be expected to be positive due to colonization in a substantial number of patients.

Because of the uncertainties surrounding blood cultures obtained from vascular catheters, the clinical utility of these cultures has been evaluated. In one study that used blinded assessments by infectious disease experts to determine the presence of true bacteremia, catheter-drawn cultures had a

sensitivity of 89%, compared to 78% for peripheral cultures, with a positive predictive value of 63% for catheter-drawn cultures versus 73% for percutaneous cultures (34). The results of that study were similar to those of other studies, leading many to suggest that if cultures are obtained from a catheter, at least one set should be drawn percutaneously (13, 20, 38, 74, 76, 92). The advantage of drawing a percutaneous culture to aid the interpretation of catheter-drawn cultures was mathematically evaluated by Tokars in a modeling study of coagulase-negative staphylococcal bacteremia (139). Tokars found that when two of two cultures were positive, the positive predictive value would be 98% if both samples were obtained through the vein, 96% if one sample was obtained through a catheter and the other was obtained through a vein, and only 50% if both samples were obtained through a catheter (139). Other studies, however, have not found a significant difference between results of catheter-drawn and peripheral cultures (39, 125, 158). If it is in fact true that blood cultures obtained from vascular catheters are more likely to be contaminated than percutaneously obtained cultures, the reason may be that sterilizing catheters prior to accessing them is more difficult than sterilizing skin or that catheter colonization is confounding catheter-drawn culture results (151).

One instance in which multiple sets of cultures are often not obtained is in NICU infants for whom the removal of too much blood is of concern and difficulty obtaining peripheral cultures is a reality. Indeed, in a survey of 35 NICUs, 83% of clinicians drew only one blood culture when a catheter-drawn sample was unavailable (105). In that same study, if blood was able to be obtained from a catheter, 224 (80%) of 279 clinicians said that they would obtain at least two blood cultures, including at least one from a peripheral vein; 37 (13%) would obtain a single culture through the central venous catheter; and 18 (6%) would obtain a single blood culture from a peripheral vein. Because of these concerns in the NICU population, antimicrobials that are active against coagulase-negative staphylococci (usually vancomycin) are often overutilized in the NICU. When practice habits from 35 NICUs were evaluated, 47 to 85% of clinicians completed a full course of antimicrobials when a single blood culture was obtained and grew coagulase-negative staphylococci, whereas a significantly lower percentage (22 to 47%) completed a full course when one of two blood culture sets grew coagulase-negative staphylococci (105).

Role of Information Technology: Automated Classification of Positive Blood Cultures

In recent decades, health information technology has played an increasingly important role in the field of infectious disease. Infection control activities are extremely data intensive, and health care information technology offers tremendous potential for improvements in the efficiency of surveillance and reporting systems. Health care institutions are increasingly turning to data-warehousing technologies to support these activities (23, 47, 109, 157). With respect to the challenge of blood culture contamination, investigators have explored automated, computer-based approaches for the classification of culture results as likely contaminants or pathogens. Such an approach offers at least two potential benefits: assisting clinical interpretation and decision-making in the face of ambiguous culture results and providing objective, reproducible, cost-efficient approaches to surveillance of nosocomial infections and bloodstream infection rates. In addition, such methods are almost always significantly faster, as they do not rely on manual identification of positive blood cultures or subsequent labor-intensive review of potentially incomplete or unavailable clinical data.

From the standpoint of surveillance, differentiating contamination from true bacteremia is essential for the accurate measurement of nosocomial bloodstream infection rates. Automated approaches to this task have been shown to perform very well compared with infection control practitioners (ICP) applying the traditional NNIS criteria (56, 141, 161). Yokoe et al. demonstrated that an automated approach for detecting nosocomial infections that relied solely upon microbiology data agreed with an NNIS-based retrospective assessment by ICP 91% of the time for cultures of adult patients (161). Disagreements were due primarily to situations in which only a single positive culture had been identified. In this scenario, CDC definitions rely on additional clinical data such as patient findings or treatment information, while the automated approach relied on a subsequent positive culture within a 5-day period. As a result of this difference in approach, 5/65 cultures were labeled as contaminated by the automated approach and as true bacteremia by the NNIS definition. In pediatric patients, agreement was found only 50% of the time, suggesting that its utility in this population may be limited. Graham et al. specifically studied the ability of a similar system in the neonatal population (47). They examined the performance of an automated system for detecting nosocomial bloodstream infections in two neonatal intensive care units in support of infection control activities. They found that their sensitivity and specificity for detecting such infections were 79% and 96%, respectively, although when coagulase-negative staphylococci were excluded, those numbers rose to 84% and 99%.

Trick et al. focused on the evaluation of a computer-based approach for detecting hospital-acquired, CVC-associated bloodstream infections (141). A comprehensive comparison of prospective ICP review, retrospective investigator assessment, and various computer algorithms was conducted on positive blood cultures from adult patients. Making this determination required several specific steps, including (i) the appropriate classification of hospital-acquired infection versus infection present upon admission, (ii) the correct ascertainment of true bacteremia versus contamination, (iii) distinguishing primary versus secondary infections, and (iv) detection of CVC use. The automated rules varied with respect to the inclusion of medication data and the time period over which data were used by a given rule. Those authors found that their computer-based algorithms performed at least as well as the ICP assessment and in fact outperformed them when combined with a manual determination of CVC use. When they looked specifically at the classification of pathogens versus contaminant organisms, a computer-based algorithm that included both microbiology data as well as pharmacy data had a sensitivity and specificity of 77% and 73%, respectively. The use of microbiology data only resulted in a drop of sensitivity to 55%.

Other investigators focused on the automated classification of blood culture results in order to provide clinical decision

support by estimating probabilities of contamination and displaying this information to clinicians at the point of care. Wang et al. utilized a previously validated prediction model (14) and revised it to include only readily available electronic data (146). By eliminating clinical data such as blood pressure, temperature, etc., they found only a slight degradation in the performance of the model. They then implemented a clinical rule into the laboratory information system to display the probability information along with blood culture results. In a subsequent house staff survey, they found that half of the respondents indicated that the results had influenced their assessment of the probability of true bacteremia, and 98% indicated a desire to continue to receive the reports. These findings suggest that computer-based approaches offer not only benefits for surveillance activities but also an opportunity to change physician behavior for individual patients. Other investigators have also shown that models that use only readily available electronic data perform well in correctly predicting contamination (100).

PREVENTING CONTAMINATION

By definition, the specificity of the blood culture is directly related to the rate of false-positive results, which are caused primarily by contamination. Reducing contamination rates would lead to improved specificity and better performance of this important test. Unfortunately, there has been a dearth of blinded, randomized, controlled trials that might provide clear and compelling guidance on the best methods for the prevention of contamination. While few would claim that the complete elimination of contamination is possible, a number of efforts to reduce contamination rates have been explored, advocated, and utilized. Factors that have been explored for reducing contamination include skin preparation, culture bottle preparation, single versus double needle for bottle inoculation, source of culture (catheter versus percutaneous), the use of dedicated phlebotomy teams, and the use of commercial blood culture collection kits.

Skin Preparation

The most common source of contaminated percutaneous blood cultures is often thought to be the skin of the patient at the site where the cultures are obtained. One study attempted to find the source of coagulase-negative staphylococcal contaminants by performing molecular analysis to compare each blood isolate to isolates obtained from swabs of the patient and from the individual who obtained the cultures (144). Of 19 patients with contaminated cultures, six of the isolates were able to be matched to swabs, and all six matching swabs came from the patient, implying that the most common source of contamination is the patient's own skin flora. However, it is important that no matching sources were found for 13 of the 19 isolates.

Skin antisepsis cannot entirely prevent the contamination of blood cultures from skin flora because as many as 20% of skin-associated bacteria have been found to survive disinfection, as found by culturing skin samples harvested with a sterile surgical technique (21, 116). These skin bacteria can be located in deep layers of the skin or in other structures that antiseptics cannot penetrate. Nonetheless, inadequate skin preparation is thought to be the most common cause of blood culture contamination (30, 89, 147).

Many studies have been performed to determine the best skin antiseptic product to use for blood culturing. Perhaps the most commonly studied and traditionally used skin antiseptic for blood culturing is povidone-iodine, an iodophor. Three studies have found significantly lower contamination rates using iodine tincture compared with povidone-iodine (67, 113, 131), although two of those studies did not have standardized phlebotomy protocols and drying times for the antiseptics. The CAP Q-Probes study investigators found that the median contamination rate was significantly lower in settings where tincture of iodine was used (2.1%) versus an iodophor (2.6%) ($P = 0.036$), but these differences were not found in organizations that relied on a dedicated phlebotomy service, suggesting that contamination may be more related to technique than the actual antiseptic used (113). One study of chlorine peroxide versus povidone-iodine found contamination in 22 (1.3%) of 1,639 cultures in the chlorine peroxide group compared to 37 (2.3%) of 1,637 in the povidone-iodine group ($P = 0.065$) (125). Another study found that 0.5% chlorhexidine plus alcohol had significantly lower contamination rates than standard povidone-iodine (82). In contrast, two studies that compared chlorhexidine to tincture of iodine did not find a statistically significant difference in contamination rates between the two products (11, 140).

Alcohol-based products are also frequently utilized for skin preparation for blood cultures. Calfee and Farr performed a randomized comparative trial of four skin antiseptics for 12,692 percutaneous blood cultures—10% povidone iodine, 70% isopropyl alcohol, tincture of iodine, or povidone-iodine plus 70% ethyl alcohol (25). The overall contamination rate was 2.62% during the study period. The contamination rates were 2.93% with povidone-iodine, 2.58% with tincture of iodine, 2.50% with isopropyl alcohol, and 2.46% with povidone-iodine plus 70% ethyl alcohol ($P = 0.62$). Although there were no significant differences between the groups, those authors concluded that the antiseptics that contained alcohol may have had greater efficacy. Other studies that examined the difference between alcohol solutions and iodine were unable to detect a statistically significant difference in contamination rates (64, 119).

Several barriers can prevent the skin antisepsis technique from being effective for preventing contamination. The time required for the antiseptic to have maximal effect is an important consideration, since the agent with the most efficacy will not be effective if the time required to become effective is longer than clinically feasible. Individuals who draw blood cultures may not have knowledge of the minimum contact time for their chosen skin antiseptic, or circumstances may not allow a sufficient drying time. For example, povidone-iodine preparations require 1.5 to 2 min of contact time to have a maximal antiseptic effect, whereas tincture of iodine requires 30 s (151). This difference in time to effect may account for differences seen in many of the aforementioned studies as opposed to a clear difference in efficacy. Although controversial, some experts recommend that the culture site be prepped with 70% isopropyl or ethyl alcohol and allowed to air dry and that a

second prep should be performed using 1 to 2% tincture of iodine or 10% povidone-iodine (30, 71).

Culture Bottle Preparation

Although data are limited, it is standard practice to disinfect the tops of the culture bottles before inoculating them with blood (30). The rubber stopper on each bottle is not sterile despite being covered with a lid that requires removal prior to inoculation. In the CAP Q-Probes study of 640 institutions, investigators found that 95.5% of organizations routinely applied an antiseptic to the top of the culture bottle before inoculating the bottle (113). Those institutions that prepped the bottle tops had significantly lower contamination rates (2.3%) than those that did not prep the bottle tops (3.4%) ($P = 0.018$).

It has been recommended that individuals should not use iodine alone because it may cause erosion of the rubber stopper during incubation, thereby introducing contaminants. Some institutions use alcohol, whereas others use an iodine solution that is allowed to dry and is then wiped off with fresh alcohol prep prior to inoculating the bottle (36).

Single Needle versus Double Needle

Until the late 1980s, discarding the needle used to draw blood cultures and using a new, different needle to inoculate the bottles (double-needle technique) was standard practice. This was based on the theory that the needle used for phlebotomy may be contaminated, thereby leading to blood culture contamination. However, with the emergence of human immunodeficiency virus, this practice became questionable, as the process of changing needles was felt to increase the risk of needlestick injuries to phlebotomists. Confirmation of the risk associated with this procedure was shown in studies revealing that most (42%) needlestick injuries occurred after use and before disposal of the naked needle, and transferring specimens from one container to another with a hollow-bore needle has been responsible for 5% of needlestick injuries (134). Subsequently, since 1990, the double-needle technique has been discouraged in favor of using the same needle to draw blood and to inoculate the culture bottles (single-needle technique).

The effect of the double-needle technique versus the single-needle technique on blood culture contamination rates has been evaluated by several controlled studies (7, 31, 54, 60, 66, 114, 124, 136). For each of these studies, the authors admitted to inadequate power to detect the level of difference that was actually observed between the two techniques. In order to improve power, a meta-analysis of these studies was performed, and it was concluded that the double-needle technique did in fact decrease contamination rates from 3.7% to 2.0% ($P < 0.001$) (126). Furthermore, the 1997 CAP survey of 640 institutions found that the median contamination rate was 2.2% in settings where the double-needle technique was used (42% of institutions), compared to 2.7% in settings where a single needle was used, but this difference was not statistically significant (112).

At the time of publication, each study's authors reasonably concluded that any benefit from the double-needle technique did not outweigh the risk of needlestick injuries. However, since the publication of those studies, the risk of needlestick injury during phlebotomy has decreased, partially due to modern safety needles (134). Additionally, vacuum-activated transfer devices have been developed to prevent the necessity of using a hollow-bore needle to inoculate blood culture bottles, which allows phlebotomists to engage the safety mechanisms on safety needles immediately after withdrawal from the patient. It remains to be seen whether these newer, safer technologies will reinvigorate the controversy about any potential relative benefits of the double-needle technique.

Obtaining Cultures Percutaneously instead of via Vascular Catheters

As stated above, cultures obtained from vascular catheters can be quite difficult to interpret. However, this technique remains a very common practice for many reasons. Many clinicians seek to prevent inflicting pain on patients by drawing cultures from a catheter instead of percutaneously. Others may wish to decrease the likelihood of inducing transient bacteremia by phlebotomy, especially for highly immunosuppressed patients. For the neonatal population, the difficulty of venous access is a real problem. Finally, practitioners may fear causing nosocomial volume depletion or anemia by drawing too many blood cultures, a potential issue with neonates or profoundly anemic patients.

Despite these good intentions, there are many undesirable consequences of this practice. The consequences could include the requirement for more cultures for clarification, more diagnostic studies, or the unnecessary use of antibiotics with the associated potential for allergic reactions, unanticipated drug interactions, or adverse drug events. Additionally, if falsely positive culture results from vascular catheters are misinterpreted, unnecessary and prolonged vascular access for intravenous antibiotics may be a consequence.

Phlebotomy Team

Trained phlebotomy or blood culture teams have been found to decrease blood culture contamination rates (132, 150, 151). In one study at a community teaching hospital, blood cultures drawn by a dedicated blood culture team using a commercially available kit had a contamination rate of 1%, as opposed to cultures drawn by resident physicians, which had a contamination rate of 4.8% using the same kit. They compared the costs of this team to the cost savings associated with a reduction in contamination rates and reported a net savings of $40,000 over a 6-month period (150). Investigators in the CAP Q-Probes study found that contamination rates were 3.9% at institutions where more than half of all blood cultures were collected by resident physicians, versus 2.2% at institutions where less than half of all blood cultures were obtained by resident physicians (112). In the more recent Q-Tracks study, there was a statistically significant difference in contamination rates between institutions that utilized a dedicated phlebotomy team versus other staff for culture collection. Institutions in which the large majority of cultures were drawn by nursing staff had a contamination rate of 4.21%, while those institutions in which those same individuals did not collect any culture specimens had a contamination rate of 2.17% (17). Dedicated

phlebotomy teams are increasingly common in the inpatient setting; in a study of 640 institutions, Schifman et al. noted that, on average, 70% of cultures were collected by phlebotomy teams at teaching institutions, while 85% of cultures were collected by such teams at nonteaching hospitals (113).

For those facilities that have not invested in the establishment of a dedicated phlebotomy team, another method that could be used is monitoring and feedback of contamination rates to the collectors. Weinstein performed a pilot study that monitored phlebotomists' contamination rates on a monthly basis. Those results revealed a contamination rate of 3% for phlebotomists compared with nearly 11% for blood cultures obtained by resident physicians, nondegree nursing assistants, and nurses (151). Monitoring and feeding back contamination rates to individuals who obtain blood cultures were used successfully in at least one other institution that achieved a 50% reduction in contamination rates using this methodology (45). Many institutions are using this technique, as indicated in the CAP Q-Probes survey, which found that 47% of laboratories stratified contamination rates on the basis of individual phlebotomists (112).

Commercial Blood Culture Collection Kits

Whether commercially marketed blood culture collection kits reduce infection rates has been debated. In one teaching hospital, cultures drawn by resident physicians who used a commercial kit had a contamination rate of 4.8%, compared to 8.4% for residents who did not use the kit (150). Kits have been found to be beneficial in other studies as well (112). Another study compared povidone-iodine pledgets and alcohol pledgets to a collection kit containing breakable ampules of alcohol and 2% iodine tincture and found no difference in contamination rates when commercial kits were used (156).

SUPPORTING OPTIMAL USE OF BLOOD CULTURES

Blood cultures are frequently ordered tests. Unpublished data from our own academic health center, which includes a 565-bed tertiary hospital with approximately 30,000 admissions per year, suggest that over 20% of our hospitalizations involve at least one blood culture. The high utilization of blood culture testing can be partially attributed to two important reasons: the difficulty that most clinicians have in predicting the risk of bacteremia (72, 80, 97) and their low threshold for ordering the test, given the significant risk of morbidity and mortality associated with this condition (15, 147, 155). Additionally, for some specific clinical conditions, such as patients admitted to the hospital with community-acquired pneumonia, professional or governmental organizations have recommended universal blood culture testing (73). As discussed above, the pretest probability for bacteremia greatly influences the positive predictive value of a blood culture result. Accordingly, several investigators have developed and evaluated clinical prediction rules for bacteremia in a wide variety of patient populations in an effort to assist decision-making regarding diagnostic workup and management. The scientific community has also assessed the rates of bacteremia in a wide variety of patient populations to better understand disease prevalence, potentially allowing the development and refinement of consensus guidelines for specific clinical scenarios.

Clinical Prediction Models

Accurate clinical bacteremia prediction models have the potential to improve the use of blood culture testing and to aid in the interpretation of indeterminate culture results by providing pre- and posttest probabilities (12). Prediction models are generally developed using two consecutive analyses: an initial derivation step that is used to determine the independent predictors of the outcome of interest, which is followed by a validation set that is used to test the model in another population. For a prediction model to be maximally useful, it should be applicable to other settings (148). Researchers have developed or studied models for predicting bacteremia in hospitalized adults (12, 65, 72, 80, 85, 88, 160) and adult patients seen in emergency departments (40, 120, 159). Similar efforts have been explored in pediatric populations, although the motivation for many of these models is targeted primarily at decision-making regarding hospital admission versus outpatient management and initiation of empirical therapy and not whether or not to obtain blood cultures (3, 4, 8, 61, 70, 99). In recent years, greater attention has been paid to the impact of contamination rates on the utility and effectiveness of the blood culture test and the implications for its use in pediatric patients (9, 63, 115, 130, 138).

In hospitalized adults, clinical prediction rules for bacteremia have been found to have mixed results, at least from the perspective of the potential for reducing unnecessary blood cultures. Bates et al. developed a model that grouped patients into four different levels of bacteremia risk based on a combination of clinical and laboratory findings (12). In this prospective cohort study, they found that patients in the lowest risk category had a 1% chance of having bacteremia in the derivation set and a 2% chance in the validation set. In this low-risk group, the positive predictive value of a positive culture was 18%. Leibovici et al. developed a similar model that focused on evaluation of newly admitted febrile adults and found the prevalence of bacteremia in the low-risk groups to be 5% in the derivation set and 1% in the validation set (65). In an attempt to test these models outside their originating institutions, Yehezkelli et al. studied the accuracy of both the Bates and Leibovici prediction models in two hospitals (academic and community) in Israel. They found that the accuracy of both models "deteriorated significantly," with misclassification rates in the low-risk groups of 13 to 15% using the Bates model and 7 to 8% using the Leibovici model (160). Mylotte et al. attempted to validate Bates' model in a different institution with similar patients and found a slight degradation in performance, with a 3% misclassification rate for low-risk patients (88). Misclassification rates for low-risk groups in models developed by other investigators ranged from 4.6 to 5.1% (80, 85, 148). As several of the authors of those studies acknowledged, such results may be insufficient for reducing blood culture testing. Indeed, based on one survey of 149 physicians that included house staff and infectious disease specialists, investigators concluded that the sensitivity of a clinical prediction rule for bacteremia would have to be extremely high (99 to 100%) to be widely accepted.

Bacteremia prediction modeling in the emergency department setting has been studied as well (40, 120, 159). Shapiro et al. described a general clinical prediction rule for bacteremia in the emergency department setting that identified low-risk groups that were associated with a 0.8% and 1.8% risk of bacteremia (derivation and validation populations, respectively) (120). The sensitivity of the model was 98% in the derivation model and 96% in the validation model. While such prediction rules may well prove clinically useful for decision-making regarding hospitalization or the initiation of empirical antibiotic therapy, it remains unclear whether or not such tools will reduce unnecessary blood culture use.

Population Studies of Bacteremia Prevalence

Efforts to ascertain bacteremia prevalence in specific subpopulations have the potential benefit to inform the appropriate use of diagnostic tests such as blood cultures. In the pediatric population, investigators have studied the risk of occult bacteremia, given the widespread adoption of vaccinations to prevent infection caused by *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (1, 9, 130). In a study of well-appearing, highly febrile children aged 2 to 36 months, Stoll and Rubin found that the incidence of occult bacteremia was 0.91% (95% confidence interval, 0 to 1.9%) and concluded that universal blood culture testing in this population may be unnecessary (130). In a recent similar study, Herz et al. conducted a retrospective review of blood cultures obtained from children aged 3 to 36 months during a 5-year period from 1998 to 2003 at Kaiser Permanente Northern California ambulatory facilities (52). Bacteremia rates dropped from 1.62% to 0.71% from the first year to the last year of the study period, while the contaminant-to-pathogen ratio increased from 1.2:1 to 2.3:1, leading the authors to agree with Stoll and Rubin about the decreased role for blood culture testing in highly febrile children in this age group, who are otherwise well-appearing and were previously healthy. The necessity of blood cultures remains controversial, however. Other investigators who studied occult bacteremia rates in similar age groups (although using somewhat different inclusion/exclusion criteria) found slightly higher rates of 1.9 to 3%, prompting them to suggest obtaining blood cultures and deferring treatment pending culture results (9).

The emergency department is another setting that has received significant attention in terms of blood culture utilization, bacteremia prevalence, and the impact of blood cultures on patient management. Innes et al. (53a) found that during a 6-month period at a hospital in British Columbia, blood culture results for patients seen in the emergency department were rarely helpful, with only 2.1% of 767 culture episodes yielding "potentially helpful" information. Similarly, in a retrospective study of 1,350 patients who had blood cultures taken in the emergency department (and who were subsequently discharged) of a large U.S. urban teaching hospital, only 0.52% had results that potentially affected their management. The prevalence of bacteremia in that population was 1.8%, leading those authors to conclude that specific criteria were needed to help guide the decision regarding blood culture testing (131a).

Finally, the question of whether or not all patients hospitalized for community-acquired pneumonia require pretreatment blood cultures, as recommended by consensus guidelines (73, 91), has become intensely debated in recent years (20a, 52a). Fueling the controversy are increasing reports suggesting that due in part to a combination of high contamination rates and low bacteremia risk, the PPV for blood cultures is low and test results are often clinically unhelpful (26, 27, 29, 33, 137). Consequently, investigators have attempted to develop specific bacteremia prediction rules for community-acquired pneumonia patients to help guide decision-making surrounding the use of blood cultures (81, 149). Metersky et al. developed a model that stratified patients into three different groups on the basis of their bacteremia risk and concluded that their tool would lead to a 38% reduction in blood culture utilization while missing 11% of individuals with true bacteremia (81). It remains to be seen whether such a model can be incorporated into routine practice.

While controversy remains in each of these areas about the proper criteria for blood culture testing and initiation of antibiotic therapy, many agree that the combination of low pretest probability (i.e., disease prevalence) with high contamination rates often leads to unhelpful culture results.

BLOOD CULTURE CONTAMINATION IN THE PEDIATRIC POPULATION

Contaminated blood cultures are a particular challenge for infants and children for several reasons. While an in-depth discussion of the topic is beyond the scope of this review, evidence suggests that contamination occurs more frequently in this population, particularly in young infants (78, 92, 101, 135). In addition, concerns about the risk of occult bacteremia have led to guidelines recommending the use of blood cultures and empirical therapy, particularly in children less than 3 years of age (10). As described above, however, the tides may be starting to turn, as the past decade has seen multiple studies suggesting that in the current era of influenza and pneumococcal vaccination, the risk of occult bacteremia has significantly lowered. As a result, the use of blood culture testing in this patient population is associated with a lower positive predictive value. Moreover, analysis of current practice patterns reveals that in most cases, only single blood cultures are collected (93, 105, 111). In an effort to reduce unnecessary discomfort, pediatricians often use existing intravenous catheters for obtaining cultures instead of peripheral venipuncture (105). The data on the impact of this practice on contamination rates are mixed. In a 2-year observational study comparing contamination rates for culture specimens drawn via venipuncture to those for culture specimens drawn via intravenous catheters in children, Norberg et al. found a large, statistically significant decrease in the rate of false-positive blood cultures (9.1% to 2.8%) after their institution adopted a policy eliminating the use of intravenous catheters for this purpose (92). While compelling, conclusions based on that study are limited by its design, which lacked a control group to account for any potential confounders such as temporal trends. Ramsook et al. found similar results in a 6-month study of 2,431 pediatric blood cultures, with contamination rates of 3.4% for specimens collected via intravenous catheters versus 2.0% for those obtained by separate venipuncture ($P = 0.043$) (101). While

that study used a large sample size, details of the study design and methods are somewhat unclear, making it difficult to ascertain both internal and external validity. Other studies have shown no difference in contamination rates according to specimen collection routes (55, 124). Given pediatricians' disinclination to subject children and infants to unnecessary painful procedures, and the lack of clear evidence on which approach best prevents specimen contamination, the use of existing catheters for blood culture collection continues in this patient population (79). As described above, single blood cultures are particularly common in pediatric patients; this fact, combined with the increased utilization of catheter-based culture specimens, makes discrimination between true bacteremia and contamination challenging, particularly when coagulase-negative staphylococci are grown in culture (24). To combat this challenge, investigators have explored multiple avenues, including the use of C-reactive protein, time to positivity, quantity of growth, and clinical status (3, 18, 19, 32, 44, 98, 110, 129). While none of these factors have performed well enough individually to warrant widespread adoption, they continue to be under investigation.

CONCLUSION

Clearly, progress has been made on several fronts in the battle against blood culture contamination. Better strategies for preventing contamination in the first place are being established, and we are improving our ability to distinguish contamination from true bacteremia. New research on measures to estimate the pretest likelihood of bacteremia offers promise in reducing unnecessary blood culture utilization. Despite the progress that has been made, however, significant barriers remain. Without a gold standard for truly distinguishing contaminant organisms from true pathogens, studies that seek to measure the success of prevention strategies are inherently limited. Similarly, efforts to help establish the posttest probability of bacteremia given a positive result are restricted. Genomic and proteomic approaches for identifying bacteremia are being explored but remain in the early stages (96, 122, 123). There is evidence, however, to suggest that even these methods can be hampered by problems with contamination (95). Furthermore, additional research on the value of time to positivity and quantity of growth for differentiating culture contamination from bacteremia is necessary. Of the various prevention strategies, additional investigation would help to determine the relative effect of each strategy on overall contamination rates. In the meantime, information technology may have a role in facilitating the detection of contamination, assisting clinical decision-making, and enabling better systems for tracking contamination rates both within and between institutions. Additional research on how to make these tools more useful and more acceptable in the clinical work environment is needed. Similarly, while clinical prediction rules for bacteremia have received much scrutiny in the past 15 years, it remains unclear whether they perform at a level that is accurate enough to influence physician behavior and affect blood culture utilization. More research is needed to refine these models and test them in other settings. In the pediatric arena, additional studies are clearly needed to help physicians interpret the results of single blood cultures that grow coagulase-negative staphylococci, a persistent challenge. Ultimately, blood culture contamination is a complex, challenging problem that requires a multidisciplinary approach. Well-conceived and effectively implemented strategies are important for reconciling the sometimes contradictory requirements of individual patient care, population health, and effective resource allocation.

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